BioDrugs (2015) 29:365–372
DOI 10.1007/s40259-015-0147-0

CURRENT OPINION

The Diversity of Biosimilar Design and Development: Implications for Policies and Stakeholders

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Published online: 18 November 2015

Abstract Biosimilars are required to be similar or highly similar in structure to their biologic reference product but are neither expected nor required to contain identical active substances. For example, glycosylated biosimilars approved to date demonstrate quantitative and qualitative structural differences from their reference product and exemplify the latitude of variations permitted for biosimilars. Although differences between a candidate biosimilar and its reference product will be evaluated for differential clinical effects during biosimilarity assessment, it is unlikely that potential differences between any two indirectly related biosimilars will be formally evaluated. Furthermore, biosimilar pathways permit variations in pharmaceutical attributes, clinical development approaches, and regulatory outcomes, resulting in further diversity of attributes among approved biosimilars. Because biosimilars may vary across the ranges of structural and functional acceptance criteria, they should not be treated like multisource, generic drugs.

Key Points

Although biosimilars are highly similar to their reference products, they are not identical to them.

Regulatory pathways permit slight differences in structural and other product quality attributes of biosimilars; such difference are unlikely to be formally evaluated among indirectly related biosimilars, resulting in a potential for a broader range of potential differences in quality attributes among approved biosimilars.

Policies and practices related to the identification and use of biosimilars should take into account potential molecular differences among multiple biosimilars of the same reference product and should not treat them like generics.

Specific recommendations to distinguish biologics from generic drugs in practice include ensuring that all biologics have distinguishable names and are prescribed by a distinguishable name, that a clinician is involved in decisions to switch among non-interchangeable biologics, and that patient medical records track biologics by their distinguishable names.

1 Introduction

Biologic medicines consist of mixtures of structural isoforms (e.g., glycoforms), whereas the active ingredient of a chemically synthesized drug is typically a single entity with a defined structure [1]. Unlike generic products for chemically synthesized drugs, which contain the same active ingredient

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as their reference product, biosimilar products do not contain active drug substances identical to their reference product [2–4]. Minor structural differences between biosimilars and their reference product are expected and allowed because of their inherent molecular complexity and differences in manufacturing processes among biologics manufacturers [4]. However, such minor structural differences are expected not to result in functional or clinically meaningful differences in terms of quality, safety, or efficacy [3].

Beyond the implications for potential differences in drug substances, biosimilar development pathways also include opportunities and incentives for diversity in drug product and clinical attributes, including formulations, presentations, devices, indications, and routes of administration [5]. Although these features also apply to chemically synthesized drugs, the nature of the biosimilars pathway may tend to promote more diversity in these aspects to compensate for the intrinsic molecular heterogeneity and intellectual property. Because biosimilars differ from chemically synthesized drugs in many critical aspects, policies and practices applicable to generic drugs from multiple manufacturers generally are not directly transferable to biosimilars [4, 6, 7].

This brief report highlights examples of structural variances (i.e., at the level of the drug substance) of biosimilars approved in the European Union (EU) and Japan to illustrate that biosimilarity is not transitive. We also provide an example of how interactions between structural attributes could be relevant to the design of a biosimilar. The biosimilar approval process relies on a comparison of one biosimilar candidate with one reference product, whereas multiple biosimilars of a given reference product can be expected in the marketplace. Therefore, we suggest that policies and practices related to the identification and use of biosimilars take into account the potential molecular differences between biosimilars and their reference products and the lack of transitivity among multiple biosimilars of the same reference product. Specific recommendations to distinguish biologics from generic drugs in practice include ensuring that each biologic has a unique name and that it is prescribed by that unique name, that a clinician is involved in decisions to switch among non-interchangeable biologics, that patient medical records track biologics by their unique names, and that reimbursement claims systems use a unique code for each individual biosimilar.

2 Differences Between Biosimilars and Reference Products Necessitate Product-Specific Identification

A review of glycosylated biosimilars approved in the EU and in Japan demonstrates that structural variances exist between biosimilars and their reference products (Table 1). For example, with Retacrit® (epoetin zeta; SB309), an EU-approved biosimilar of Eprex®/Erypo® (epoetin alfa), the extent of glycoforms without an O-linked glycan chain was found to be higher in the biosimilar than in the epoetin alfa reference product [8]. Conversely, levels of variants of sialic acid (N-glycolylneuraminic acid and O-acetyl neuraminic acid) were higher in the reference product [8]. Independent studies, as well as our internal analysis (Table 2) performed after Retacrit® (epoetin zeta) was approved in the EU, have revealed additional structural differences, including higher levels of lactosamine repeats and lower levels of sialylation relative to Eprex® (epoetin alfa) [9]. As an example of diversity in drug product formulation or presentation, differences in potency between these products have also been reported, with the biosimilar product demonstrating 8 % lower bioactivity relative to the reference product, likely due to a difference in protein concentration [8].

Another EU-approved biosimilar of Eprex®/Erypo® (epoetin alfa), Binocrit® (epoetin alfa; HX-575), contains higher levels of phosphorylated high mannose glycans (mannose-6-phosphate glycans) at one glycosylation site, Asn-24, and lower levels of sialic acid (N-glycolylneuraminic acid and diacetylated neuraminic acid) than the reference product [10]. Independent studies, as well as our internal analysis (Table 2), performed since Binocrit® was approved, have revealed additional structural differences, including higher levels of Lewis-X structures relative to Eprex® (epoetin alfa) [9]. No differences in bioactivity between Eprex® (epoetin alfa) and Binocrit® (epoetin alfa) were noted in their respective development studies [10].

The first biosimilar monoclonal antibody approved in the EU, a biosimilar of Remicade® (infliximab) marketed under the trade names Remsima™ (infliximab; CT-P13) and Inflectra™ (infliximab), displays lower levels of afucosylated glycan structures relative to the reference product [11]. These differences correlate with lower binding affinity for the fragment crystallizable (Fc) receptors Fc_{γ}RIIIa and Fc_{γ}RIIIb, which mediate certain immunologic functions [11]. Further, the biosimilar displays lower antibody-dependent cell-mediated cytotoxicity in certain in vitro assays [11]. In addition, Ovaleap® (follitropin alfa; XM17), a biosimilar of Gonal-f® (follitropin alfa) approved in the EU, demonstrates differences in sialic acid content and an increase in nonhuman sialic acid variants with N-glycolylneuraminic acid, in comparison with the reference product [12]. Bemfola® (follitropin alfa), another biosimilar of Gonal-f® (follitropin alfa), also manifests minor differences from the reference biologic in its glycosylation profile [13]. For the biosimilar, the ratio of tetra-antennary:di-antennary structures was slightly higher, there were slight differences in the distribution of fucosyl residues in relation to antennarity, and sialic acid residues of

Table 1 Structural variances of approved biosimilar products in the European Union (EU) and Japan

Approved biosimilar	Reference product	Regulatory region	Structural differences relative to reference product
Retacrit® (epoetin zeta; SB309)	Eprex®/Erypo® (epoetin alfa)	EU	Higher levels of glycoforms lacking occupied O-glycan site [8]
			Lower levels of N-glycolylneuraminic acid and O-acetylneuraminic acid [8]
Binocrit® (epoetin alfa; HX-575)	Eprex®/Erypo® (epoetin alfa)	EU	High Man-6-P levels detected in clinical study batches [10]
Remsima™ (infliximab; CT-P13)	Remicade® (infliximab)	EU	Lower levels of afucosylated variants [11]
Ovaleap® (follitropin alfa; XM17)	Gonal-f® (follitropin alfa)	EU	Slight shift in sialic acid content and increase in nonhuman sialic acid variants with N-glycolylneuraminic acid [12]
Bemfola® (follitropin alfa)	Gonal-f® (follitropin alfa)	EU	Minor differences in glycosylation profile [13]
			Ratio of tetra-antennary:di-antennary structures slightly higher [13]
			Slight differences in distribution of fucosyl residues in relation to antennarity [13]
			O-acetyl–containing sialic residues of α-subunit below level of detection [13]
Epoetin alfa BS injection [JCR] (epoetin kappa)	Espo® (epoetin alfa)	Japan	Isoforms of higher molecular mass [14]
			Additional basic isoforms [14]

JCR Japan Chemical Research Pharmaceuticals Co., Ltd., *Man-6-P* mannose-6-phosphate glycans

Table 2 Reported and independently assessed differences in glycation attributes between two epoetin biosimilars and their reference product, Eprex® (epoetin alfa)

Attribute	Retacrit® (epoetin zeta)		Binocrit® (epoetin alfa)	
	EPAR	Amgen data	EPAR	Amgen data
O-glycans				
Occupancy	Lower	Lower	–	Similar
Sialylation	–	Lower	–	Higher
N-glycans				
Sialylation	–	Lower	–	Similar
Lactosamines	–	Higher	–	Similar
Lewis-X structures	–	Similar	–	Higher
Phosphorylated high mannose	–	Similar	Higher	Higher
Sialic acids				
Total/epoetin	–	Lower	–	Similar
NGNA variant	Lower	Lower	Lower	Lower
Acetylated	Lower	Lower	Lower	Lower

EPAR European public assessment report [8, 10], *NGNA* N-glycolylneuraminic acid

the α-subunit contained an O-acetyl group not detected in the reference biologic [13].

An independently developed epoetin biosimilar product licensed to Japan Chemical Research Pharmaceuticals Co., Ltd. (JCR), "Epoetin alfa BS injection [JCR]; epoetin kappa," has been approved in Japan. This biosimilar has isoforms of higher mass (likely due to increased lactosamine extensions) and additional basic isoforms (due to lower levels of sialylation) in comparison with its reference product, Espo® (epoetin alfa) [9, 14].

In our laboratories, we have used animal models to study the effects of lactosamine extensions and N-glycan sialylation on epoetin potency. Increases in N-glycan branching and sialylation have previously been correlated with increased epoetin potency, primarily due to their effect on the epoetin serum half-life [15, 16]. Our studies showed that increased lactosamine extensions also increase epoetin potency and that increased levels of lactosamines could be compensated for by reduced levels of sialylation (unpublished data). This multifactorial design and

characterization challenge has been characterized in a guidance document published by the US Food and Drug Administration (FDA), using the example of lactosamines and sialylation [17]. In light of two examples of approved epoetin alfa biosimilars with elevated lactosamine and reduced sialylation, it is apparent that biosimilar development is more complex than simply matching all critical quality attributes to within the reference product range. Rather, it is a holistic design problem, and each biosimilar may represent a unique solution to that problem.

All biosimilar products mentioned here have been developed through a comprehensive similarity exercise, which included analytical, nonclinical, and clinical comparisons with their reference product, and the results were reviewed by the regulators according to their respective regulatory frameworks prior to their approval. In the view of the approving regulators, it is unlikely that these structural differences will result in clinically meaningful effects on efficacy and safety in the approved indications; however, these differences in product attributes exemplify the latitude in structural variance permitted in biosimilars. Future development of additional biosimilars to the same reference product may bring additional structural diversity as some sponsors introduce alternative host cell expression systems in their manufacturing processes. In addition, once biosimilars are approved, manufacturing changes to either the biosimilar or the reference product could result in evolution of quality attributes outside the ranges that were assessed during biosimilar development [18]. However, there is no requirement to prove biosimilarity again as a result of product life-cycle management.

The existence of such structural differences between biosimilars and their reference biologics, as well as between separately developed biosimilar products of the same reference product, warrants accurate identification of the specific drug or active substance. This could be accomplished by assigning distinguishable names to all biologics, including biosimilars. Such names could be a combination of distinguishable nonproprietary names and/or mandatory trade names to clearly identify biologics manufactured by independently developed processes. Given that the FDA has no authority to require brand names for biosimilars and that some prescribers and prescribing systems may prefer nonproprietary names, it may be advisable to assign a distinguishable nonproprietary name to each biosimilar. Specific product identification is important in prescribing and dispensing drugs and in maintaining patient medical records, and it allows accurate attribution of adverse events to the correct product and the relevant manufacturer during postmarketing pharmacovigilance [19–21].

3 Biosimilarity Is Not Transitivity

The relationship between a given biosimilar product and its reference product is not transitive to other biosimilars. This is a natural consequence of the fact that biosimilars are not structurally identical to their reference biologic products or to each other. Each biosimilar differs from its reference product in its own unique manner and is permitted to differ in terms of quantitative and qualitative structural aspects as a result of differences in manufacturing processes [3]. Indeed, there is no regulatory requirement to ensure that all biosimilars of a particular reference biologic differ in a similar qualitative manner or to the same extent. The manufacturing details and history of the originator reference product will be unknown to the biosimilar sponsor. Therefore, biosimilar sponsors must independently characterize the reference product, evaluate biosimilarity in the context of the equivalence window (i.e., the range of product quality attributes that was established by the biosimilar sponsor during the evaluation for its licensure [18]), and establish postapproval controls. It should be noted that product quality attributes of the biosimilar are not necessarily required to fall within the same range of variability as the reference product and that the biosimilar equivalence window and the proven acceptable range of quality attributes of the reference product, each justified independently to regulatory agencies, are likely to differ (Fig. 1) [18].

For recombinant human erythropoietins, glycosylation has been linked to in vivo biologic activity, and certain features of N-linked glycan heterogeneity are considered critical quality attributes [22]. Glycoform profiling of three epoetin reference products and three epoetin biosimilars, using liquid chromatography/mass spectrometry–electrospray ionization, has shown a unique characteristic pattern of glycoforms for each product [9]. Additionally, a principal component analysis, using liquid chromatography/mass spectrometry to assess glycan heterogeneities among nine recombinant epoetin products, found that four epoetin biosimilars did not plot close to the reference biologic, indicating relative differences in glycan heterogeneities [22]. These data demonstrate that not only do the epoetin biosimilars differ from the reference product in glycosylation but also the difference among biosimilars can be greater than the difference between each biosimilar and the reference drug. Further, these data demonstrate that biosimilars have multidimensional structural heterogeneity and proprietary quality specifications, and they lack transitive properties of identity.

The practical implication of biosimilar diversity is that biosimilars should not be used in practice in the same manner as multiple-source (i.e., multisource) generic drugs. Multisource drugs are a set of generic equivalents to

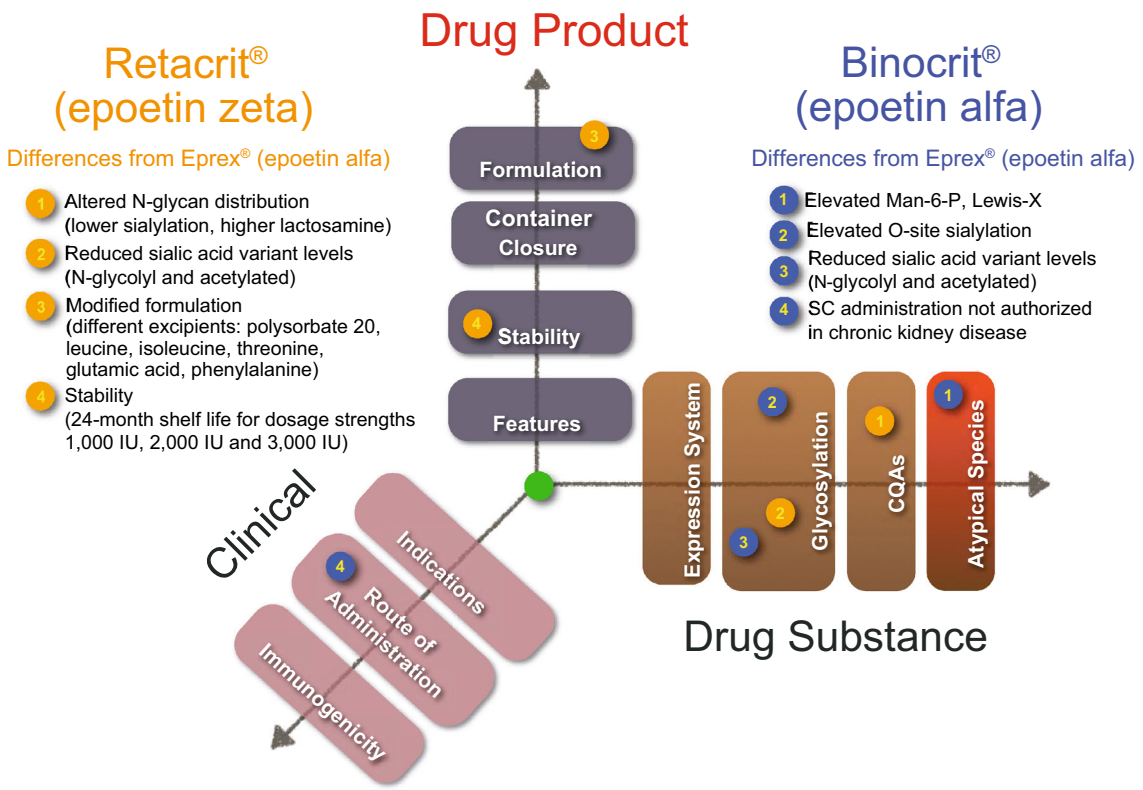

Fig. 1 Biosimilar 1 ≠ biosimilar 2. Retacrit® (epoetin zeta) and Binocrit® (epoetin alfa), biosimilars of Eprex®/Erypo® (epoetin alfa), differ substantially from each other in multiple parameters [8, 10, 33]. The elements of a drug substance are shown on the *x* axis (i.e., the expression system, glycosylation, critical quality attributes [CQAs], and new or atypical species). The elements of a drug product are shown on the *y* axis (i.e., the formulation, container closure, stability, and other features). The clinical elements are shown on the *z* axis (i.e., the indications, route of administration, and/or immunogenicity profile). The *green dot* represents the reference product. The *blue dots* represent the differences between the reference product and Binocrit®. The *orange dots* represent the differences between the reference product and Retacrit®. Difference in this context means either new product variants (quality attributes) not found in the reference product, or product variant/attribute levels outside the range of the reference product. *Man-6-P* mannose-6-phosphate glycans, *SC* subcutaneous

a given brand drug [23]. In the USA, multisource drugs are commonly treated as an interchangeable commodity for which a prescriber need not select any particular version (i.e., prescribing by generic name is encouraged), and switching among generic equivalents is commonly practiced at the pharmacy level without prescriber awareness or involvement. In the USA, multisource drugs administered under a medical benefit typically receive the same drug billing and payment code, reflecting their status as an interchangeable commodity [24]. Furthermore, adverse event reports are often assigned to the product class or are misattributed to the originator brand [7, 25].

None of these generic drug practices are advisable for biosimilars. Availability of multiple biosimilar versions of a single biologic reference product is expected as the biosimilar industry matures; this is already a reality for some product classes in Europe. To avoid inadvertent switching and to ensure traceability of adverse events to the appropriate biologic or biosimilar, EU policymakers have emphasized that they should be prescribed and tracked by unique names (typically brand names) [21]. In the USA, the first biosimilar has been given a distinguishable nonproprietary name (i.e., filgrastim-sndz) to facilitate pharmacovigilance and prevent inadvertent switching [26]. Policymakers have also emphasized that clinicians should be involved in decisions to switch patients from one biologic to another, although an exception may be made in the USA for a biosimilar determined by the FDA to be interchangeable with its reference product [27]. These policies have been recommended in recognition of the complex relationship between a given biosimilar and its reference product, but they are also relevant when one considers the undefined relationships among a set of similar biologics (i.e., multiple biosimilars of a single reference product). Another practical implication of biosimilar diversity is that each biosimilar product administered under the outpatient

medical benefit should have a unique reimbursement code to facilitate traceability of adverse events to a particular manufacturer via active surveillance tools such as the FDA's Sentinel program [28].

4 Other Sources of Diversity

We have focused primarily on the sources and consequences of structural diversity of biologics at the level of the drug substance. Beyond these considerations, biosimilar sponsors may also consider options for different formulations, containers, or devices to improve shelf-life, handling, or convenience to patients or healthcare providers [5, 29]. For example, biosimilar filgrastim and follitropin alfa products approved in the EU have been developed with different formulations and/or strengths relative to their reference products and to each other [30–36]. Formulations and containers can, in turn, influence structural attributes and stability profiles of biologics, potentially creating additional sources of variation in the physicochemical attributes of the active substances administered to patients [37].

Furthermore, biosimilar developers may be granted a subset of the clinical indications or other conditions of use (e.g., routes of administration) of the reference products [5]. These considerations are not unique to biologics, but when they are coupled with the diversity of development choices for design of drug substances and drug products, it is likely that a given set of related biosimilar products could possess a diverse and nontransitive collection of structural, pharmaceutical, and clinical characteristics. In such circumstances, it may not be appropriate to view the entire class as a set of fully interchangeable therapeutic equivalents but, rather, as therapeutic alternatives. There is nothing derogatory toward biosimilars in this observation; it is merely a reflection of the practical reality of the nature of biosimilar development and the incentives for individual choices in commercialization and life-cycle management.

Current regulations do not require multiple biosimilars to be similar to each other, nor do they require a given biologic to remain similar to any other biologic over time. Therefore, cumulative changes in the relative levels of N-glycan sialylation and lactosamine repeats due to planned changes (i.e., product evolution) or unknown deviations (i.e., drift) in manufacturing processes of any of the erythropoietins could potentially result in a difference in the required dose for a given patient among various epoetin products [18]. Similar opportunities for divergence in functionally relevant product attributes could emerge for other classes of glycosylated biologics, including monoclonal antibodies subject to future biosimilar competition.

5 Conclusions

Regulatory pathways for biosimilars anticipate and allow for flexibility in the nature and composition of structural variants and other attributes of biosimilars. Although this flexibility is critical for the successful development of new biosimilars, the range of variability for quality attributes of a biosimilar may not fall within the same range accepted for the reference product. As biosimilars of more complex reference products have been developed (e.g., glycosylated erythropoietins, follitropins, and monoclonal antibodies), there has been no decrease in the prevalence of structural and quality differences [8, 10, 12, 13]. The examples summarized above demonstrate that similarity may not be transitive to other biosimilars of the same reference product. Because the specifications for posttranslational modifications and other quality attributes of a biosimilar will likely vary from those of the reference product, owing to the complexity of biologics and their manufacturing processes, biosimilars should not be considered to have the "same" active substance as their reference product or other biosimilars of the same reference product. Although differences in structure between a candidate biosimilar and its reference product will be evaluated in functional, nonclinical, and clinical studies to assess biosimilarity and to demonstrate the lack of clinically meaningful differences, the potential differential clinical effects between any two biosimilars of the same reference product will not likely be formally evaluated. Specific differences or combinations of differences relative to the reference product may not exceed the bounds of a clinically meaningful effect on safety or efficacy, but the cumulative effect of differences between biosimilars might have a clinically meaningful effect. Because biosimilars vary from their reference biologic product and from each other in quality attributes and possibly in other pharmaceutical and clinical attributes, they should not be treated like generics from multiple manufacturers. Rather, they should be considered as individual therapeutic alternatives. In practice, this means that biosimilars should each be assigned a unique name, they should be prescribed and tracked in medical records by a unique name, and clinicians should be involved in decisions to switch patients among similar biologics, particularly when the FDA has not determined a given biosimilar to be interchangeable with the prescribed biologic.

Acknowledgments The authors acknowledge the contributions of Gary Camblin (Amgen Manufacturing Limited), Patricia L. McElroy (Amgen Inc.), and Vanessa Torres De Leon (Amgen Manufacturing Limited) toward the generation of data used in the characterization of the structure and biologic function of epoetins. The authors acknowledge Patrick Little, PhD, and James Balwit, MS (Complete Healthcare Communications, LLC), whose work was funded by Amgen Inc., for assistance in writing this manuscript.

Compliance with Ethical Standards

Conflict of interest GG and SR are employees of and own stock in Amgen Inc. GG has provided expert testimony on behalf of Amgen Inc. in support of legislation in US states that allows for automatic substitution of FDA-approved interchangeable biologic products with provisions to communicate and record the biologic product dispensed. The authors had full control of all primary data.

Funding This work was funded by Amgen Inc.

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